Depression: Identification, Evaluation and Management in Primary Care

Primary Care Update: 2013

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Prevalence and Burden of Depression

- 1/8 people in the U.S. affected
- 6.7% of U.S. population each year
- 40% have first episode before age 18
- Associated with:
  - increased overall mortality
  - increased premature CV death
  - increased morbidity – disability, decreased productivity & wages
- Leading cause of disability for 15-44 yo in US now
- Predicted 2nd leading cause disability worldwide by 2020

Primary Care Provides ½ of the Outpatient Care for Depression

- Primary care has as many visits for depression as psychiatrists
- 10% of all primary visits are depression-related
- 5-10% of primary care patients meet DSM-IV criteria for major depression
- 3-5% meet criteria for Dysthymia
- 10% criteria for minor depression
- Estimated that 10-20% of patients with chronic medical illness (heart disease, DM) meet criteria for major depression
Primary Care Should Screen All Adults
It’s Easier Than You Think

- USPSTF*, ACPM, AMA, ACOG, AAFP all recommend (“when “systems in place””)
- Two questions only:
  - “During the past month, have you felt down, depressed or hopeless?”
  - “During the past month, have you felt little interest or pleasure in doing things?”
  - 97% sensitivity, 67% specificity
- Or, self-administered questionnaires:
  - Patient Health Questionnaire-9, Beck Depression Inventory, Zung Self-Rating Depression Scale, Center for Epidem Studies Depression Scale

Screening in Geriatric Patients

Five-item Geriatric Depression Scale —
1. Are you basically satisfied with your life?
2. Do you often get bored?
3. Do you often feel helpless?
4. Do you prefer to stay at home rather than going out and doing new things?
5. Do you feel pretty worthless the way you are now?

Scoring: Each item worth 1 point if positive. A score of 2 points or greater is considered a positive screen for depression.

Major Depressive Episode
DSM-IV-TR Criteria

At least 5 of 9 symptoms present most of the day nearly every day for a minimum of two consecutive weeks:

- Depressed mood
- Loss of interests/pleasure
- Change in sleep
- Change in appetite or weight
- Change in psychomotor activity
- Loss of energy
- Trouble concentrating
- Thoughts of worthlessness or guilt
- Thoughts about death or suicide

Additional factors in the history

- Duration of symptoms
- Degree of functional impairment
- Symptoms of anxiety, panic attacks
- Cognitive, neurological symptoms
- History of mania or psychotic symptoms
- History of trauma, abuse
- Suicide risk
- Alleviating factors, Exacerbating factors
- Medication Use
- Family History
- Alcohol and substance abuse
Distinguish Major Depression From:
- Alcohol or other substance use
- Generalized anxiety disorder
- Dementia
- Perimenopause
- Personality disorder
- PTSD
- Somatoform disorder
- Eating disorder
- Sleep disorder
- Pain
- Bipolar Disorder

Depression recurs
For most patients, relapsing and remitting course
- After 1st episode, >40% recurrence in 2 yrs
- After 2 episodes, 75% recurrence in 5 yrs

Mrs. Jess Tyred
47 yo woman, no significant PMHx
- "I'm just tired."
- new excessive fatigue but sleeps 8 hrs
- "I just wanted you to check if it's thyroid"

Do Patients Believe PCPs Can Meet Their Mental Health Needs?
- Patients report concerns about PCP knowledge, competence, and openness
- Patients report reservations about physician-patient trust but that trust is essential
- Patients report concern that their mental health is outside the bounds of primary care
- Patients may be deterred from seeking care and disclosing symptoms

You’re Running Late but You Probe

- She reports a loss of interest in her work, family life and friends.
- For past 3 months has been crying excessively, overeating and increasingly feeling her life is worthless.
- Twice in the past week she had to ask a neighbor to pick up her children from school because she was “just so tired” she couldn’t do it herself.
- You give her the PHQ-9 and scores very high

The First Step in Treatment: Patient Education

- Discuss the diagnosis directly with patient
- Emphasize depression is common and impacts the perception and impact of physical symptoms, such as fatigue
- Explain treatment generally shortens the course and reduces residual symptoms
- If patient is reluctant to accept diagnosis, observe initially, return visit soon

Remission is the Target Endpoint

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonresponse</td>
<td>&lt;25% decrease in baseline symptoms</td>
</tr>
<tr>
<td>Partial Response</td>
<td>&lt;50% (26-49%) decrease in symptoms</td>
</tr>
<tr>
<td>Response</td>
<td>Reduction in symptoms by 50%</td>
</tr>
<tr>
<td>Partial Remission</td>
<td>Most symptoms not evident but still some residual, &gt;50% decreased severity from baseline</td>
</tr>
<tr>
<td>Remission</td>
<td>No symptoms, normal functioning</td>
</tr>
</tbody>
</table>

*Patients with response but not remission have worse prognosis, higher relapse rates than full remission*

Question #1:

Mrs. Jess Tyred accepts your diagnosis of depression and is willing to be treated

What is the best initial treatment of depression?

**Depression is Treatable Condition**

“50% of Patients Get 50% Better”

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**To Take or To Talk....That is the Question**

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**Psychotherapy vs. Pharmacotherapy**

*Either Psychotherapy or Single Medication for 1st MDE:*
- 20-35% achieve remission
- 50% achieve response
- 3 RCTs of patients in primary care found drug therapy or psychotherapy similar efficacy for first MDE

*Combination Psychotherapy and Pharmacotherapy*
- Patients with recurrent or chronic major depression, data favor combination treatment
- Less severe, non-recurrent major depression, combination treatment no significant advantage over drug therapy or psychotherapy alone

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**The rise in antidepressant prescriptions**

- Associated with introduction of SSRIs in 1988
- From 1988–1994 to 1999–2002 significant rise in:
  - Comparing two time periods, the use of antidepressant drug during past month (data from self-reporting)
    - Among adults more than tripled from 2.5% to 8.0%
    - Among women rose from 3.3% to 10.6%
    - Among men rose from 1.6% to 5.2%
Mrs. Jess Tyred says her friend told her about a segment on CBS News -60 Minutes which reported that antidepressants are all actually placebo.

Are antidepressants just a placebo effect?

- Shown to be superior to placebo in thousands of controlled clinical trials in 5 decades
- Magnitude of the benefit increases with severity of depression symptoms
- Substantial benefit for patients with severe depression
- The milder the depression, the more difficult it is for treatments to separate from placebo.

What’s the evidence for antidepressants in primary care?

- 2009 Cochrane review found that only 14 studies have been done comparing antidepressants (TCA or SSRI) vs. placebo in adult primary care settings
- Both TCAs and SSRIs found more effective than placebo
- More adverse reactions and withdrawal from drug on TCAs vs. SSRIs.

Question #2:
Mrs. Jess Tyred accepts recommendation for antidepressant

Of the following choices, which is the best first choice for initial episode of depression?

1. Zoloft 50 mg qd
2. Prozac 40 mg qd
3. Prozac 20 mg qd + Wellbutrin SR 100 mg qd
4. Effexor XR 150 mg qd
How to choose first antidepressant?

Second Generation Antidepressants

- Selective serotonin reuptake inhibitors (SSRIs)
- Serotonin-norepinephrine reuptake inhibitors (SNRIs)
- Serotonin modulators
- Noradrenergic and specific serotonergic antidepressant

- Citalopram
- Escitalopram
- Fluoxetine
- Fluvoxamine
- Paroxetine
- Sertraline
- Venlafaxine
- Duloxetine
- Desvenlafaxine
- Nefazadone
- Trazodone
- Mirtazapine
- Buproprion
- Mirtazapine

Major Trials
Initial Choice of Antidepressant

- Placebo Trials
- Head to Head Trials
- Feasibility Trials (STAR-D Trial)

Limitations of Antidepressant Clinical Trials

- Few head-to-head trials
  - Over 25 yrs 1980-2005, only 46 head-to-head trials between newer antidepressants
- Industry funding
  - 96% of these had an author affiliation or sponsorship by pharmaceutical company
- Publication bias
  - Of all clinical trials registered w/ FDA, 51% were positive trials
  - Of all clinical trials that were published, 94% were positive trials

NEJM Jan 17, 2008; Ann Int Med 2005

As of 4/10/13 12:04
SSRIs

- Usual first line choice
- Fairly safe in Overdose
- More similar than different in trials
- Individuals respond differently to differentiate SSRI.

SSRIs: 3 phases of potential side effects

- Early onset and frequently transient (last 1-2 wks)
  - Common are nausea, GI upset, lightheadedness, headache, jitteriness
- Early onset and persistent:
  - sexual symptoms – decreased libido, erectile function, ejaculatory function, sexual responsiveness
  - Men and women
- Gradual onset and accrue:
  - weight gain (typically not more than 10 lbs)

Strategies for the initial side effects

- “Start low and go slow”
- Reassurance
- Explain, education for expectations
  - Fast onset of side effects but transient, slow onset of benefits
- For anxiety, jitteriness
  - add low-dose benzodiazepines, short term

Venlafaxine (Effexor)

- Mixed NE and SHT activity
- 3% have increased blood pressure
- similar side effect profile to ssri’s
- significant withdrawal syndrome when stopping
- 50% reduction in perimenopausal hot flashes
- Example of initiating:
  - Effexor XR 37.5 mg /day x 7 days then Effexor XR 75 mg /day
  - After 4-8 weeks, can increase to Effexor XR 150 mg/day

Duloxetine (Cymbalta)

- Mixed NE and 5HT activity
- Alleviates pain of diabetic neuropathy and fibromyalgia
- Used independently for pain management
- Start at 20 mg or 30 mg/day
- Increase to 60 mg/day - 90 mg/day


Bupropion (Wellbutrin)

- Low rate of sexual side effects or weight gain
- At high doses, can see weight loss
- Assoc. w/ increased rate of seizures
- Used in smoking cessation (Zyban)
- Safe and effective to combine with SSRI or SNRI
- 3 formulations:
  - short acting (TID)
  - SR (BID)
  - XL (qdl)
- Example of starting wellbutrin:
  - Wellbutrin SR 100 mg d x 7 days then 100 mg BID
  - If tolerates, transition to Wellbutrin XL 150 mg qday
  - Can increase to wellbutrin XL 300 mg q day

Mirtazapine (Remeron)

- Sedating
- Significant weight gain potential
- Faster onset of action than SSRIs, SNRIs, Wellbutrin
- Example of initiating:
  - Remeron 15 mg tab – ½ tab qhs x 2 weeks, increase to 15 mg qhs
  - Can be used in combination with SSRI or SNRI

Consider associated symptoms

- Panic attacks, anxiety ------------------SSRI, SNRI
- Insomnia------------------------Mirtazapine or Paroxetine
- Sexual dysfunction----------------------Bupropion
- Weight management-------------------Bupropion
- Hot flashes---------------------------Venlafaxine
- Compulsive behaviors-------------------SSRI
- Pain, neuropathy---------------------Duloxetine
**Relative Activation**

<table>
<thead>
<tr>
<th>Type</th>
<th>Medications</th>
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<tbody>
<tr>
<td>Activating</td>
<td>Bupropion, Fluoxetine, Sertraline</td>
</tr>
<tr>
<td>Neutral or mixed</td>
<td>Venlafaxine, Escitalopram, Citalopram</td>
</tr>
<tr>
<td>Mildly to moderately sedating</td>
<td>Paroxetine, Nefazadone, TCAs</td>
</tr>
<tr>
<td>Sedating</td>
<td>Trazadone, Mirtazapine</td>
</tr>
</tbody>
</table>

**Relative Effect on Sexual Functioning**

<table>
<thead>
<tr>
<th>Type</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased</td>
<td>Bupropion</td>
</tr>
<tr>
<td>Neutral or mixed</td>
<td>Nefazadone, Mirtazapine, Duloxetine</td>
</tr>
<tr>
<td>Common</td>
<td>SSRIs, Venlafaxine, TCAs, MAOIs</td>
</tr>
</tbody>
</table>

**Relative Weight Gain Potential**

<table>
<thead>
<tr>
<th>Type</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss (?)</td>
<td>Bupropion</td>
</tr>
<tr>
<td>Neutral or mixed</td>
<td>Nefazadone</td>
</tr>
<tr>
<td>Mild to moderate gain</td>
<td>SSRIs (Fluoxetine &lt; Paroxetine)</td>
</tr>
<tr>
<td>Significant</td>
<td>Mirtazapine, MAOIs, TCAs</td>
</tr>
</tbody>
</table>

**Comparative Efficacy and Acceptability**

**Lancet 2009**

- **Efficacy** = 50% symptom reduction week 8
- **Acceptability** = dropout during first 8 wks
- Multiple treatments meta-analysis
- 117 head-to-head randomized trials and 26,000 patients

**Educational Techniques For Patients Starting Antidepressants**

- Do not stop meds w/o discussing first
- A lag of weeks before symptoms relieved
- Certain early side effects occur in first days-week, most gone within 1-2 week
- Call if side effects or questions
  - 72% patients discontinue by 90 days
- Exercise, positive activities
- Consider addition of psychotherapy

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**Mrs. Jess Tyred: Visit 2 and 3**

- After 6 weeks on Zoloft 50 mg she reports 20% improvement in symptoms and no side effects. You increase her dose to 100 mg.
- After another 6 weeks on Zoloft 100 mg qd, she now feels 40% improved and no side effects.
- She still has not called any psychotherapists - saying “I'm sure it would help but I just don’t have the time or the money.”

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**Typical Starting and Target Doses**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Start mg/d</th>
<th>Usual mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram (Celexa)</td>
<td>10-20</td>
<td>20-60</td>
</tr>
<tr>
<td>Escitalopram (Lexapro)</td>
<td>10</td>
<td>10-20</td>
</tr>
<tr>
<td>Fluoxetine (Prozac)</td>
<td>10-20</td>
<td>20-60</td>
</tr>
<tr>
<td>Paroxetine (Paxil)</td>
<td>10-20</td>
<td>20-60</td>
</tr>
<tr>
<td>Sertraline (Zoloft)</td>
<td>25-50</td>
<td>50-200</td>
</tr>
<tr>
<td>Buproprion (Wellbutrin)</td>
<td>75-150</td>
<td>300</td>
</tr>
<tr>
<td>Buproprion SR (Wellbutrin SR)</td>
<td>100</td>
<td>300</td>
</tr>
<tr>
<td>Buproprion XL (Wellbutrin XL)</td>
<td>150</td>
<td>300</td>
</tr>
<tr>
<td>Venlafaxine XR (Effexor XR)</td>
<td>37.5-75</td>
<td>75-300</td>
</tr>
<tr>
<td>Duloxetine (Cymbalta)</td>
<td>30</td>
<td>60-120</td>
</tr>
<tr>
<td>Mirtazapine (Remeron)</td>
<td>15</td>
<td>15-45</td>
</tr>
</tbody>
</table>

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**Escitalopram and Sertraline Superior in both efficacy and tolerability**

4 Most Effective
1. Escitalopram (Lexapro)
2. Mirtazipine (Remeron)
3. Sertraline (Zoloft)
4. Venlafaxine (Effexor)

4 Most Tolerable
1. Buproprion (Wellbutrin)
2. Citalopram (Celexa)
3. Escitalopram (Lexapro)
4. Sertaline (Zoloft)

*Considering cost, sertraline may be best 1st choice.*

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*Cipriani, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. The Lancet: 373; 9665, Feb 28 2009; 746-758*

Question #2
With her partial response (40%), what is next?
A. Switch within the SSRI class (e.g., Zoloft to Lexapro)
B. Switch from SSRI to SNRI (e.g., Zoloft to Effexor XR)
C. Augment with 2nd med (e.g., Zoloft + Wellbutrin)
D. Add psychotherapy, wait 6-8 weeks to reassess med

The STAR*D Trial: Feasibility Trial
- Level 1: Celexa
- Level 2: Patients choice to either switch or augment
  - SWITCH
    - randomized to Bupropion SR, Venlafaxine XR, Zoloft, or CT
  - AUGMENT
    - randomized to Buproprion SR, Buspirone, CT
- Level 3: Patients choice to either switch or augment
  - SWITCH
    - randomized to Mirtazapine or Nortriptyline
  - AUGMENT
    - randomized with Litium or T3 thyroid hormone
- Level 4:
  - SWITCH
    - randomized to Trancypromine or Mirtazapine + Venlafaxine XR
CT = Cognitive Therapy

STAR*D: With Partial Response, Switching or Augmenting is Reasonable
- Augmentation may be preferred if pt is tolerating and receiving partial benefit from initial medication
- Augmenting with Buproprion SR is recommended over buspirone for tolerability and high symptom improvement
- Switching within-class or out-of-class is effective

STAR*D: Adjust Antidepressants Since Good Chance Achieving Remission
- 50% achieve remission by 2nd regimen
- 70% achieve remission by 4th regimen
- 10-30% have resistant depression
Mrs. Jess Tyred
Choices in the Real World

- Effexor XR is not covered by her insurance
- You offer 2 choices
  1) continuing Zoloft and adding Wellbutrin
  2) stopping Zoloft and switching to Lexapro
- Mrs. Tired chooses Lexapro, because
  “My sister took Lexapro and it worked for her”
  “I don’t want to take 2 medications”

Does Patient Preference Matter?

- Patients’ requests have a profound effect on physician prescribing in major depression
- Direct-to-consumer (DTC) advertising of prescription drugs is ubiquitous
- Patients’ treatment preference and treatment received influenced the development of the therapeutic alliance
- Response by a first degree relative may be a factor to consider in choice of drug

Question #3
Which is not an appropriate method to switch from Zoloft 100 mg to Lexapro 10 mg?

A. Instruct patient to stop Zoloft 100 mg today and start Lexapro 10 mg tomorrow (switch)
B. Taper down the Zoloft while simultaneously tapering up the Lexapro (cross-taper)
C. Slowly taper off the Zoloft, allow a 2 week wash-out period, then taper up the Lexapro (taper and wash-out)

Mrs. Jess Tyred
Side Effects

- You make a direct switch from Zoloft 100 to Lexapro 10 mg and Mrs. X returns after 6 weeks.
- She now feels “almost 100% better,” and is relieved to “feel herself again.”
- You check in about side effects. She hesitates at first, then reports decreased libido.
Do antidepressants really differ in their side effects?

- The profiles of adverse events are similar among second-generation antidepressants.
- But the incidence rates of specific adverse events differ.
- Drop out rates are different

Management of SSRI Sexual Dysfunction

- Can develop after weeks to months
- Occurs in 30-70% of patients on SSRIs
- Buproprion has fewer sexual dysfunction adverse effects

Mrs. Jess Tyred
How Long Should She Be Treated?

- Because of the sexual side effects, you add Wellbutrin XL 150 mg qd in order to reduce the Lexapro to 5 mg qd. Her libido improves and has a stable mood.
- She remains on the 2 drugs for 18 months and then wants to “try stopping.” She tapers off with temporary difficulty but then felt fine.
- One year later, she felt a relapse of her depression.

Duration of Antidepressants?

- Recommend at least 6-9 mo treatment of 1st episode
- Relapse is common once patients stop
  - Restart same treatment with the same therapy which induced remission with prior episode
- Maintenance therapy can decrease rate of relapse
  - 31 RCTs in metaanalysis of maintenance vs. placebo found relapse of 41% vs. 19%
- Maintenance therapy recommended if history of 3 or more depressive episodes, 2 episodes + risk factors of recurrence
Combination therapies: Usual examples

- **SSRI + Buproprion**
  - Example: Zoloft 100 mg + Wellbutrin XL 150 mg

- **SNRI + Buproprion**
  - Example: Effexor XR 150 mg + Wellbutrin SR 100 mg BID

- **SNRI + Mirtazipine**
  - Example: Effexor XR 150 + Remeron 15 mg qhs

- **SSRI/SNRI + Benzo (during initial 4 weeks SSRI tx)**
  - Example: Lexapro 10 mg + Klonopin 0.5 mg BID

- **SSRI/SNRI + Buspirone**
  - Example: Celexa 40 mg + Buspar 10 mg TID

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Stepwise Rationale Approach

1) Diagnosis, screen for comorbid conditions

2) Weigh choices of treatment options - therapy, antidepressant, both or other

3) Initial antidepressant choice (SSRI typically first line – zoloft or lexapro) - start low and go slow

4) Evaluate effectiveness and tolerability at week 4-6.

5) If partial response, then adjust dose, add 2nd medication, or switch

6) Continue treatment minimum of 6-9 months.